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NEXT GENERATION OF NUTRACEUTICALS

Introduction:

In last few decades, the role of active components of diet in human nutrition and health has become an important focus of research. A new product category that has emerged from it is 'nutraceuticals'. The term "nutraceutical" was coined in 1989 by Stephen De Felice, founder and chairman of the Foundation for Innovation in Medicine, an American organization which encourages medical health research. He defined a nutraceutical as a "food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease".

Nutraceutical is a term derived from "nutrition" and "pharmaceuticals." The term is not defined the same in different countries, but is usually defined as a product isolated from foods that is generally sold in medicinal forms not usually associated with food. A nutraceutical product has physiological benefit or provides protection against chronic diseases. Nutraceuticals may be used to improve health, delay the aging process, prevent chronic diseases, increase life expectancy, or support the structure or function of the body.

Broadly nutraceutical product categories are divided into two major ones:

1. Functional Foods & Beverages
2. Dietary Supplements

Functional Foods

Functional Foods are foods that provide health benefits beyond the provision of essential nutrients, when consumed at efficacious levels as part of a regular diet. These types of foods provide added physiological benefits, potentially reducing chronic, commonly encountered disease risks or otherwise optimize health.

Institute of Medicine, USA defines functional foods as any food or food ingredients that may provide health benefit beyond the traditional nutrient it contains.

Some instances of Functional Foods are Omega-3 enriched eggs, Fortified – margarines, Iodized salts, Probiotic yoghurt etc

Functional Beverages

Functional beverages are non-alcoholic beverages containing ingredients that provide specific health benefits beyond those of

general hydration. Traditionally, beverages have been fortified with vitamins, minerals, amino acids and antioxidants. Examples of Functional Beverage include performance and sports drinks, enhanced water, energy drinks, and soy beverages and enhanced fruit drinks.

Dietary Supplements

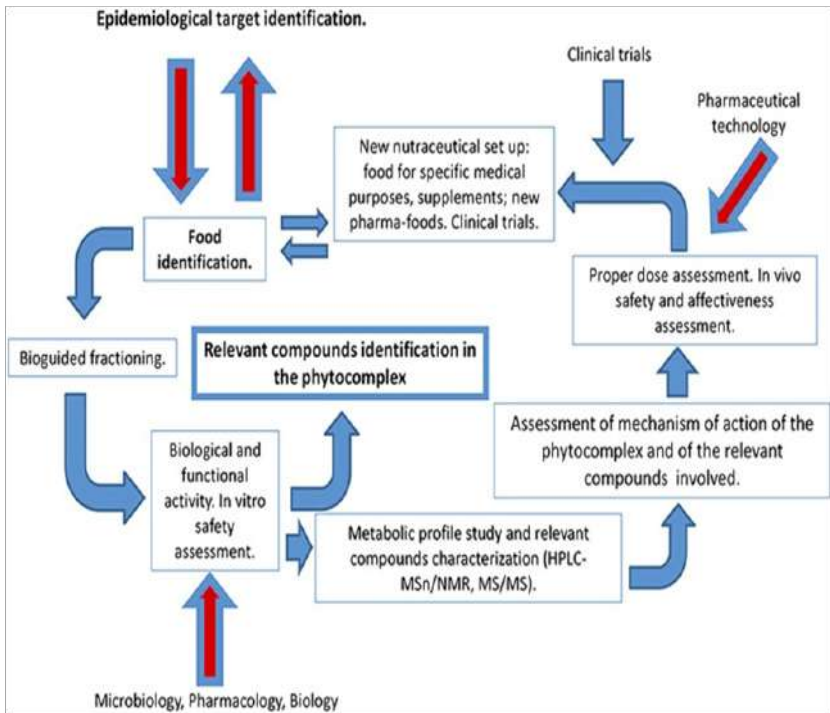
A dietary supplement is a product intended for ingestion that contains a “dietary ingredient” intended to add further nutritional value to (supplement) the diet, which may otherwise not be

consumed in sufficient quantities. Examples of dietary supplements are Vitamins, Minerals, Amino Acids, protein supplements and herbal supplements.

Development of next generation nutraceuticals:

A nutraceutical should have strong scientific evidence substantiating the claimed health effect and should have proven efficacy and safety, before its use in clinical practice.

Any new Nutraceutical should undergo below mentioned Development Pathway:



Next Generation of neuro-protective nutraceuticals:

Aging is a major risk factor for a number of neurodegenerative disorders. These age-related disorders currently represent one of the most important and challenging health problems worldwide. Therefore, much attention has been directed towards the design and development of neuroprotective agents derived from natural sources. These phytochemicals have demonstrated high efficacy and low adverse effects in multiple *in vitro* and *in vivo* studies.

Palmitoylethanolamide (PEA):

Palmitoylethanolamide (PEA) is a naturally occurring fatty acid amide. PEA has emerged as a potential nutraceutical, because this compound is naturally produced in many plant and animal food sources. PEA is endowed with important neuroprotective, anti-inflammatory and analgesic actions.

PEA is efficacious in mast cell-mediated models of neurogenic inflammation and neuropathic pain and is neuroprotective in models of stroke, spinal cord injury, traumatic brain injury, and Parkinson disease. PEA in micronized/ultramicro-nized form shows superior oral efficacy

in inflammatory pain models when compared to naïve PEA. Intriguingly, while PEA has no antioxidant effects *per se*, its co-ultramicro-nization with the flavonoid luteolin is more efficacious than either molecule alone.

Luteolin

Luteolin is an important flavone, which is found in several plant products, including broccoli, pepper, thyme, and celery. Numerous studies have shown that luteolin possesses beneficial neuroprotective effects both *in vitro* and *in vivo*.

Curcumin, Resveratrol, Genistein

Alzheimer's disease (AD) is regarded as a progressive and devastating neurodegenerative disorder. In aged individuals, it is the most prevalent cause of dementia and is characterized by gradual loss of cognitive functions. Although the etiology of AD is still not clear, several histopathological studies confirm prominent changes in the AD affected brains. The major changes include the formation of senile plaques and neurofibrillary tangles primarily owing to the deposition of amyloid β plaques (A β) and hyper-phosphorylation of tau protein. Disruption of the

redox homeostasis in the brain is a major triggering factor for the development of such pathophysiological conditions.

Multipotent natural compounds curcumin, resveratrol and genistein have the ability to interfere with the formation as well as deposition of the A β peptides. These natural compounds have also been found in modulating different intracellular signalling molecules and enzymes including β -secretase and γ -secretase.

Next Generation Bioactive Peptides:

Bioactive peptides are specific protein fragments derived through enzymic hydrolysis of food proteins. There is an abundance of bioactive peptides contained in a wide range of food sources (products of plant, animal and marine origin).

The results obtained from in vitro and in vivo studies of bioactive peptides have shown they have potential as treatments of numerous diseases or risk factors.

Brief description of few promising bioactive peptides present in milk and different plants is as follows.

Milk bioactive Peptides

Milk is one of the richest sources of proteins and bioactive peptides. Milk bio-peptides have been shown to have BP lowering, cholesterol lowering, anti-inflammatory and immunomodulatory actions.

The tripeptides, valine-proline-proline (VPP) and isoleucine-proline-proline (IPP) are contained in milk in large amounts. A meta-analysis of 18 randomized clinical trials, have reported that these peptides lower systolic BP by 3.73 mmHg and diastolic BP by 1.97 mmHg.

Whey proteins are also a rich source of bioactive peptides; in particular, the aspartate-arginine-valine-tyrosine-isoleucine-histidine-proline-phenylalanine-histidine-leucine (DRVYIHPFHL), aspartate-arginine-valine-tyrosine-isoleucine-histidine-proline-phenylalanine (DRVYIHPF) and arginine-valine-tyrosine-isoleucine-histidine-proline-phenylalanine (RVYIHPF). All these peptides have shown antihypertensive activity through an inhibitory action on the renin-angiotensin-aldosterone (RAS) system.

β -lactotensin is a bioactive peptide derived from milk with

cholesterol lowering action. At a dose of 100 mg•Kg⁻¹ p.o., it significantly reduced serum cholesterol in mice and increased the excretion of bile acids in the faeces.

IPP and VPP peptides, derived from the bacterial fermentation of casein, show anti-inflammatory activity; they prevent the formation of atherosclerotic plaque by inhibiting the pro-inflammatory JNK-MAPK pathway. Another polypeptide (aspartate-methionine-prolineisoleucine-glutamine-alanine-phenylalanine-leucine-leucine-tyrosine-glutamine-glutamate-proline-valine-leucine-glycine-proline-valine-arginine – DMPIQAFLLYQEPVLPVR) derived from β -casein exerts an anti-inflammatory action through the inhibition of NF- κ B pathway. In humans, the administration of proteins derived from milk reduces postprandial inflammation in obese and non-diabetic subjects, as indicated by a reduction in the serum inflammatory biomarkers monocyte chemoattractant protein-1 (MCP-1) and chemokine (C-C motif) ligand 5 (CCL5).

Lactoferrin, a whey protein, has been demonstrated, in vitro, to inhibit the growth of breast cancer (MDA-MB-231) and nasopharyngeal carcinoma cells. Studies in mouse model

in vivo confirmed its anticancer activity against head-and-neck squamous cell carcinoma and demonstrated an improvement in the chemotherapeutic effects of tamoxifen in 4 T1breast cancers.

α -lactalbumin, another whey protein has shown chemopreventive properties in vitro through the activation of apoptosis.

In addition, many peptides from casein and whey proteins also possess immunostimulatory activity.

Plant bioactive Peptides:

Peptides extracted from cereals, such as oats and barley, isoleucine-valine - tyrosine (from wheat germ) and isoleucine-aspartate-proline show a strong inhibitory action on ACE, which leads to lowering of BP. A recent meta-analysis has shown that in hypertensive patients the intake of soy isoflavones is associated with a decrease in SBP by 5.94 mmHg and of DBP by 3.35 mmHg.

Lunasin is a bioactive peptide derived from soy. Lunasin, a 43-amino acid peptide characterized by a RGD sequence followed by eight aspartate residues at its carboxyl-end, has high bioavailability and stability. Animal models and cell lines studies

showed a potential cholesterol-reducing activity of lunasin. Tests are therefore necessary to assess its efficacy and safety in clinical practice.

Apart from cholesterol lowering, Lunasin, has shown anti-inflammatory properties, probably due to the inhibition of IL-6 and IL-1 β production, activation of NF-kB Akt-mediated (interaction with α V β 3 integrin), COX-2 and inducible NOS expression and PGE2 production.

Studies have shown that lunasin exerted antineoplastic effects in breast, skin, colon, prostate, leukaemia and lymphoma cell lines through different mechanisms of action.

Lunasin has been demonstrated to scavenge both peroxy and superoxide radicals, confirming its antioxidant properties in vitro.

Besides lunasin, a pentapeptide Glutamate-Glycine-Arginine-Proline-Arginine, extracted from rice bran, demonstrated to cause the 84% inhibition of the growth of colon cancer cells (Caco-2 and human colorectal adenocarcinoma cell line, HCT-116), 80% of the growth of breast cancer cells (MCF-7, MDA-MB-231) and 84% of that of liver cancer cells (HepG-2).

Bowman-Birk inhibitor (BBI) is a bioactive peptide contained

in legume seeds. BBI has a well-characterized ability to inhibit trypsin and chymotrypsin activities and seems to have a preventive effect against prostate, breast and colon cancers.

Next generation probiotics:

Potential next-generation probiotic bacteria (members from Clostridium clusters IV, XIVa and XVIII, *F. prausnitzii*, *Akkermansia muciniphila*, *Bacteroides uniformis*, *Bacteroides fragilis* and *Eubacterium hallii*) and microbiota-derived molecules (e.g. membrane proteins, short-chain fatty acids) are being evaluated in preclinical and clinical trials to promote the development of innovative dietary supplements.

Faecali bacterium prausnitzii

Faecali bacterium prausnitzii is an extreme oxygen sensitive (EOS) bacterium belonging to the Clostridium cluster IV. Results from animal studies suggest that *F. prausnitzii* can be considered as a promising probiotic candidate for the treatment of disorders characterised by chronic gut inflammation.

Akkermansia muciniphila

Recent evidence shows that there is a link between the altered gut microbiota and metabolic diseases like obesity, diabetes

mellitus, and cardiovascular disease. Higher abundance of *A. muciniphila*, a mucin degrading microbe, was associated with improvement in blood glucose homeostasis, lipid profile, and body fat distribution. A study showed that administration of *A. muciniphila* could reverse the atherosclerotic lesions, improve metabolic endotoxemia-induced inflammation, and ultimately restore the gut barrier.

Bacteroides fragilis* and *Bacteroides uniformis

B. fragilis produces polysaccharide A (PSA), which is an immunomodulatory molecule that activates the T-cell dependent immune responses. Furthermore, *B. fragilis* activates Toll-like receptor (TLR) pathways.

Oral administration of *Bacteroides uniformis* (*B. uniformis*) CECT 7771 in high fat diet-fed mice improved lipid profile, reduced glucose, insulin and leptin levels, increased TNF- α production by dendritic cells and increased phagocytosis. Thus, administration of *B. uniformis* CECT 7771 can ameliorate metabolic disorder and immunological dysfunction related to intestinal dysbiosis in obese mice. Furthermore, acute administration of this strain to mice did not promote adverse effects on health status or food intake, and there was no bacteria translocation to blood, liver, or lymph nodes.

This indicates that there are no safety concerns for this strain in mice, but further investigation should be completed in humans.

Eubacterium hallii

Eubacterium hallii is an important anaerobic butyrate producer resident in our gut. Butyrate has been proposed to lower mucosal inflammation and oxidative status, strengthen the epithelial barrier function, and modulate intestinal motility in addition to being an energy source for colonocytes. *E. hallii* can yield propionate from a broad range of substrates. This versatility may enhance the host-gut microbiota homeostasis. Moreover, administration of *E. hallii* in obese and diabetic db/db mice increased energy metabolism and improved insulin sensitivity. However, increasing dosage of *E. hallii* did not impact body weight or food intake, indicating that this strain is safe and effective.

Cocktails of *Clostridium* Cluster IV AND XIVA members

Clostridium spp. belonging to clusters IV and XIVA (also known as *Clostridium leptum* and *coccoides* groups, respectively) are exceptional inducers of Tregs in the colon and can be considered as therapeutic options for IBD and allergies.

SER109, is a novel biological agent proposed to restore the balance in the gut microbiome, promoting resistance to pathogenic invaders like *C. difficile*. SER-287 was developed for the treatment of ulcerative colitis. RBX2660, is a mix of live human microbes for effective treatment of recurrent CDI.

Nutrigenomics:

Great progress has been made over the past decade with respect to the application of biotechnology to generate nutritionally improved food crops. Biofortification, the delivery of micronutrients via micronutrient-dense crops, offers a cost-effective and sustainable approach to tackle micronutrient malnutrition. Bioavailable micronutrients in the edible parts of staple crops at concentrations high enough to impact human health can be obtained through breeding or through transgenic approaches. Biofortified staple crops such as rice, maize and wheat, harboring essential micronutrients are under development as well as new varieties of crops which have the ability to combat chronic disease. 'Proof of concept' studies have been published using transgenic approaches to biofortify staple crops (e.g. high beta-carotene 'golden rice' grain, high ferritin-Fe rice grain, etc).

Among the next generation of genetically modified (GM) plants are those that are engineered to produce elevated levels of nutritional molecules such as vitamins, omega-3 fatty acids, and amino acids.

Next Generation nutraceutical formulations:

Many highly hydrophobic bioactives, such as non-polar nutrients, and fat-soluble vitamins, have a relatively low or variable oral bioavailability. The poor bioavailability profile of these bioactives may be due to limited bioaccessibility, poor absorption, and/or chemical transformation within the gastrointestinal tract (GIT).

Drug delivery systems such as nano particles, liposomes, microemulsions, and polymeric implantable devices are emerging as promising options for improving bio-availability of nutraceuticals.

Nanoceuticals are nutrients that have been manufactured into nanoparticles using nanotechnology. Nutraceutical products made with nanoceuticals, help convert fat-soluble nutrients into water-soluble ones, providing complete and uniform nutrient absorption, and also help them pass through membranes directly into human cells.

Microencapsulation of nutrients provide formulators options to prevent taste and reactivity issues, while micronization and nanotechnology make the application of insoluble minerals in beverages possible.

There has been growing interest in the use of edible nanoemulsions as delivery systems for lipophilic active substances. Oil-in-water nanoemulsions consist of oil droplets with diameters typically between approximately 30 and 200 nm that are dispersed within an aqueous medium. The small droplet size usually leads to an improvement in stability, gravitational separation, and aggregation. Moreover, the high droplet surface area associated with the small droplet size often leads to a high reactivity with biological cells and macromolecules. As a result, lipid digestibility and bioactive bioavailability are usually higher in nanoemulsions than conventional emulsions.

Nanoemulsions offer several advantages over other food systems such as the ability to incorporate hydrophilic, amphiphilic, and lipophilic excipient ingredients, high physical stability, and rapid gastrointestinal digestibility.

Two nanoemulsion-based approaches to improve bioavailability are: Nanoemulsion Delivery Systems (NDS) and Nanoemulsion Excipient Systems

(NES). In NDS, hydrophobic bioactives are dissolved within the lipid phase of oil-in-water nanoemulsion. In NES, the bioactives are present within a conventional supplement, or food, which is consumed with an oil-in-water nanoemulsion. An excipient emulsion may have no inherent health benefits itself, but it boosts the biological activity of bioactive ingredients co-ingested with it by altering their bioaccessibility, absorption, and/or chemical transformation

Research is still required to ensure these systems are commercially viable, and to demonstrate their safety and efficacy using animal and human feeding studies.

Conclusion:

In near future, many novel nutraceuticals are likely to be made available for prevention and treatment of number of different diseases. A close interaction between academia, industry and regulatory agencies is essential for developing safe and effective next generation nutraceutical products.



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